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REVIEW

Li et al: Ocular nano delivery trends

Trends in noninvasive ocular nanoparticle drug delivery: A bibliometric analysis (2004–2023)

Dan Li[1], Qing Ye[1*], Chao Li[1*]

[1]Suzhou Kowloon Hospital, Shanghai Jiaotong University School of Medcine, Jiangsu Province, China.

[*]Correspondence to **Chao Li** lichaodr@163.com and Qing Ye 39005294@qq.com

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ABSTRACT

This study presents a bibliometric analysis of research on noninvasive nanoparticle drug delivery systems for the transocular surface from 2004 to 2023. Relevant publications were retrieved from the Web of Science Core Collection. VOSviewer and CiteSpace were used to map contributions by countries/regions, authors, institutions, journals, keywords, keyword clusters, and timeline trends. A total of 695 articles were analyzed, showing a steady year-by-year increase in publications. China, the United States, and Spain were the leading contributors. Among authors, Alvarez-Lorenzo, Carmen was the most prolific, while Chanhan, Anuj's work received the most citations among the top 10 prolific researchers. The International Journal of Pharmaceutics published the highest number of articles in this field, whereas the Journal of Controlled Release was the most frequently cited among the top 10 most productive journals. The University of Santiago de Compostela and the University of Florida were among the most active institutions in this research area. Keyword analysis identified recent key themes such as controlled release, cell interaction, dry eye, mechanisms, gene expression, and ocular drug delivery. The growing interest in transocular surface nanoparticle drugs is driven by their advantages, including increased solubility, improved stability, reduced administration frequency, sustained therapeutic concentrations, enhanced corneal penetration, and prolonged ocular surface residence time.

Keywords: nanoparticle; drug delivery systems; transocular surface; bibliometric; visualization analysis.

INTRODUCTION

The ocular drug delivery systems market continues to grow globally. According to statistics, this market has maintained a steady CAGR between 2017 and 2021. This growth trend is expected to continue in the coming years and the market size will expand significantly by 2028.Topical medication remains the primary approach for treating various ocular diseases. However, traditional ocular drug delivery methods, such as eye drops, ointments, and tablets, are hindered by significant limitations, including brief drug retention times due to rapid tear drainage, limited permeability, challenges with patient adherence, and potential side effects associated with frequent dosing [1-3]. Consequently, these conventional methods often fall short of providing long-term, effective, and gentle treatment solutions for ocular surface diseases, including dry eye, infections, glaucoma, myopia, and fundus disease.

A pivotal innovation in ophthalmic diagnosis and treatment is the development of noninvasive transocular drug delivery systems, which have shown remarkable practical value and technological advancements in addressing the unique challenges associated with ocular diseases. These advancements stem from rapid progress in biomaterial science, drug formulation technology, and nanotechnology. Notably, these new delivery systems have managed to overcome the limitations posed by the unique anatomical structure of the eye, such as the corneal barrier, tear washout, and the intricate physiological environment of the ocular surface, which typically lead to poor drug absorption and limited duration of effective drug concentration[4-6].The specific features of non-invasive trans-ocular drug delivery systems include the ability to overcome anatomical obstacles in the eye, precise targeting and controlled release, improved bioavailability, and reduced loss of drug in the systemic circulation. Integrating novel nanomaterials into ocular drug delivery systems has further propelled these advancements. With unique size effects, surface properties, and drug-loading capacities, these systems enable more precise targeting, controlled release, enhanced bioavailability, and non-invasive application to the ocular surface. By analyzing the design principles, material choices, and real-world applications of

these advanced systems, we can gain a deeper understanding of their significant contributions to the advancement of ophthalmic medical technology.[2, 7-9]. Bibliometrics, a field focused on using mathematical and statistical methods to quantitatively analyze literature, originated in the 1950s through the pioneering work of Eugene Garfield, who laid the foundation for the quantitative study of scientific publications [10]. This field has since revealed essential insights into the growth patterns of scientific knowledge, collaboration networks, and citation dynamics. Today, bibliometric analysis is widely applied across various domains, including evaluation scientific research impact, calculating journal impact factor, analyzing discipline structures, and mapping research collaboration networks, thus providing objective and quantitative support for research management and decision-making[11-14]. To date, no comprehensive bibliometric review has been conducted on the research status and evolving trends in transocular surface nanoparticle drug delivery systems.The core aim of this study is to systematically analyse and summarise research on non-invasive ocular surface nanoparticle drug delivery systems between 2004 and 2023 by applying bibliometric methods. We chose this area because of its great potential and application in ophthalmic therapy, but also because of the many challenges and unknowns. This paper employs bibliometric methods to systematically organize and summarize the past two decades of research in this field, quantitatively presenting its developmental trajectory, research hotspots, and evolutionary trends. Visualization diagrams are used to outline the field's overall framework, emphasizing recent focal points and developmental trends.

MATERIALS AND METHODS

Data collection

Web of Science Core Collection was employed in this study as the data source. Because the Web Science Core Collection contains a wide range of data from multiple subject areas, it ensures a comprehensive search of the literature in the field of noninvasive nanoparticle transocular drug delivery systems. This data source has rigorously screened and reviewed the literature to ensure the accuracy and authority of

the search results.To retrieve comprehensive and precise data, the citation indexes chosen were SCI-EXPANDED and SSCI. After the initial collection of literature, we used the checking function of software such as EndNote to remove duplicate bibliographic records. By comparing key information such as titles, authors, abstracts, etc. of the literature, we ensured the uniqueness of each literature record, thus avoiding the impact of double counting on the study results.The search terms were TS = (“nanomicelles” OR “nanoparticles” OR “nanosuspensions” OR “nanoemulsions” OR “microemulsions” OR “nanofibers” OR “nanowafers” OR “exosomes” OR “hydrogels” OR “microneddles” OR “ biomaterials” OR “nano” OR “Nanomedicine” OR “micro particles”) AND TS = (“ocular surface” OR “ cornea” OR “Conjunctiva” OR “eyedrops” OR “contact lenses”). The timeframe for the search spanned from January 1, 2004, to December 31, 2023. The types of documents included were articles, and the language was English. After duplicates were removed, a total of 695 valid papers were retrieved. The screening process is illustrated in Figure 1.

Methods

Bibliometric methods with the assistance of two visualization tools, VOSviewer and CiteSpace, were employed in this study. We predominantly utilized VOSviewer (1.6.20) and CiteSpace (6.1) for generating knowledge graphs. Each software has its own strengths and can complement the other. CiteSpace utilizes a set-theoretic data standardization method to measure the similarity of knowledge units. Its similarity algorithm is employed to generate Timezone and Timeline views within a time slice, allowing for a clear delineation of the knowledge evolution process and the historical span of a particular cluster of literature, facilitating an understanding of the development process and trends in the field[15-17]. VOSviewer, on the other hand, employs a data standardization method based on probability theory and offers various visual perspectives in the areas of keywords, co-occurrence, and co-authors, including network views, overlay views, and density views, noted for their ease of mapping and visually appealing graphics[18, 19].

RESULTS

Overall research publication information

The number of publications and their trends over the years reflect the overall significance and level of attention in the field. Visualization of the publication dates of research results related to noninvasive nanoparticle drug delivery systems provides a clear perspective on the research status, temporal distribution, annual publication volume, and development process, as depicted in Figure 2. The search results show that these 695 papers originate from 58 countries, involve 916 institutions, and include 3405 authors, published across 198 journals and citing 20760 sources. Over the period from 2004 to 2023, the total number of publications has shown an overall fluctuating upward trend. Prior to 2012, the annual publication volume consistently remained below 20 papers, with fluctuations thereafter but always staying above 20 papers, peaking in 2023 with 109 papers.Through Figure 2, it can be clearly seen that the heat of research in this field is increasing year by year, indicating that more and more researchers are beginning to pay attention to and devote themselves to research in this field.

Co-authorship analysis of authors, countries, institutions, and journals

The analysis of literature authors provides insights into the representative scholars and core research forces in the field. Authors with more than three publications are defined as core authors, totaling 76, with a combined publication count of 322 papers, accounting for 46.33% of the total publications. This aligns with the half-standard proposed by Price, indicating that the field has formed a relatively stable group of author collaborations. Using CiteSpace software to identify authors in research related to nanomediated ocular drug delivery systems and plotting co-authorship networks, as shown in Figure 3, where nodes represent authors, the size of the node font is positively correlated with the author's publication count, and the connections indicate collaborative relationships between authors, with link colors corresponding to the respective publication year on the left. Different node colors represent papers published by the author in different years. Nodes with multiple concentric rings

indicate publications in corresponding years. Figure 3 visualises which authors have a high level of influence and intensity of collaboration in the field. This helps researchers to understand the academic networks and research communities in the field.Utilizing VOSviewer, an analysis showcasing high-productivity authors in the field with publications greater than the top 10 is presented in Table 1. Among the high-productivity authors, the most prolific in terms of publication count is Alvarez-Lorenzo (n=16) from Spain, with 475 citations and an average citation count of 29.69 per paper. The discovery of 'Alvarez-Lorenzo' has not only advanced the development of nanoparticle ocular delivery technology, but has also provided lessons for drug delivery studies in other organs. Through in-depth analysis of the methodology, data analysis and clinical application of the study, we realised that 'Optimisation of drug delivery systems' is crucial for achieving efficient drug delivery. These revelations provide important guidance for our research and valuable references for our future research directions.Notably, ranked second is Chanhan, Anuj, from the United States, with 14 publications, garnering 1274 citations and an impressive average citation count of 92. In third place is Concheiro, Angel, also from Spain, with 13 publications, 384 citations, and an average citation count of 29.54 per paper.

To assess which countries have made the most significant contributions in this research field, a visual analysis of the publication volume by country was conducted. Initially, countries with a publication count equal to or greater than 10 were visualized using CiteSpace. The results are shown in Figure 4, where larger nodes represent higher publication volumes, connections between nodes indicate the strength of association, with thicker lines denoting more collaborative publications between two countries, and node colors indicating publication time. Additionally, Table 2 in VOSviewer lists the top 10 countries based on publication volume and their average citation counts. Among the four countries with cumulative publication counts exceeding 50 papers, China n=220), USA (n=112), India (n=80), and Spain (n=65) stand out as the primary research forces in the field of nanomediated ocular drug delivery systems. China's research output in this field significantly exceeds that of

other countries. Nodes with a purple outer ring in the graph represent countries with high centrality. It is observed that the four countries with the highest publication volumes also exhibit high centrality, rightfully earning them the status of core research forces. Additionally, countries like England, Germany, and New Zealand, despite having lower publication volumes, show high centrality, indicating that their research output holds significant influence. Research institutes in the country have demonstrated a wide network of collaboration and formed a stable research community in nano mediated ocular drug delivery systems. Research institutes in the United States have a strong track record of innovation and technology development in ocular drug delivery systems, and maintain close collaborations with several research institutes around the world. Indian institutes have made significant progress in the use of nanotechnology for the treatment of ocular diseases, particularly in drug delivery for specific ocular diseases. Spanish institutions have a unique perspective and approach to nanoparticle design and drug delivery mechanisms.

CiteSpace software was employed to analyze the source institutions of research literature related to noninvasive nanoparticle drug delivery systems. The co-occurrence network diagram in Figure 5 show institutions with a publication count of 10 or more. In the graph, larger nodes indicate higher publication volumes for the institution, connections between nodes represent the strength of association, thicker lines indicate more collaborative publications between two institutions, and node color denotes publication time. The colour and size of the nodes give an idea of which institutions have high research output and impact in the field. At the same time, the thickness of the connecting lines reflects the intensity of collaboration between institutions. Additionally, Table 3, analyzed using VOSviewer, lists the top 10 publishing institutions and their average citation counts. The institution with the most publications is the University of Santiago De Compostela (n=29), with an average citation count of 64.10, the same institution where the top publishing author, Alvarez-Lorenzo, is affiliated. The institution with the highest average citation count is ranked second, University of Florida (n=22), with an impressive average citation

count of 93.88, the institution of author Chanhan, Anuj. At the third position is Shenyang Pharmaceutical University (n=20) located in China, with 545 citations and an average citation count of 27.25 per paper.

VOSviewer software was utilized to analyze the journals publishing research literature related to nanomediated ocular drug delivery systems, a visual analysis of all journals was conducted. The results, as shown in Figure 6, reveal that larger nodes represent journals with greater influence, while nodes of the same color indicate similarity in research areas. Table 4 showcases the top 10 journals. Journals with a publication count equal to or greater than 15 include International Journal of Pharmaceutics, Pharmaceutics, Journal of Drug Delivery Science and Technology, International Journal of Nanomedicine, Journal of Controlled Release, Drug Delivery, and International Journal of Biological Macromolecules. This indicates that these journals have significantly contributed to advancing research in this field in recent years.By analysing the research papers published in the core journals, we can find that the research papers published in the core journals explored the use of gene therapy, cell therapy and biomaterials to achieve effective treatment of ocular diseases, which indicates that with the continuous development of biotechnology and nanotechnology, new drug delivery strategies are emerging, and also provides new research ideas and directions for researchers.

Co-occurrence analysis of keywords

Keywords function as a concise representation of document content, and conducting a co-occurrence analysis on them can reveal the research hotspots in a specific field. Utilizing CiteSpace software to construct a co-occurrence network of keywords, as shown in Figure 7, nodes represent keywords, with the size of the node and its label font positively correlated with the frequency of occurrence of that keyword. Each link indicates keywords appearing together in an article, with link colors corresponding to the publication year on the left. Different node colors represent the publication years of the literature containing that keyword. Nodes with multiple concentric rings indicate that papers related to that keyword were published in the corresponding years.

The graph displays keywords with a frequency of occurrence of 30 times or more, showing that there are 32 keywords with such frequency, including drug delivery, nanoparticle, system, release, in vitro, formulation, hydrogel, contact lens, solid lipid nanoparticle, among others. Betweenness centrality quantifies the importance and influence of a node within a network by reflecting the frequency at which the node serves as a bridge along the shortest paths connecting other nodes.Keywords with centrality greater than 0.1 (keywords with a purple outer ring in the graph) are considered to have significant influence. In the context of research related to ocular drug delivery systems, keywords such as controlled release (0.19), cell (0.14), dry eye (0.13), mechanism (0.12), expression (0.12), and ocular drug delivery (0.1) exhibit high centrality, serving as key nodes in this research field.

Keyword cluster analysis and timeline graph

The keyword clustering map can help to explore the knowledge structure of research hotspots related to nanomediated ocular drug delivery systems and analyze the distribution of research topics. By automatically clustering 321 keywords, a cluster network display of keywords in the field of nanomediated ocular drug delivery systems was obtained, divided into 14 cluster modules, as shown in Figure 8. The modularity index Q was 0.7348 (Q values range from [0, 1], with values greater than 0.3 indicating significant network modular structure), and the silhouette index S was 0.8948 (S values closer to 1 indicate higher network homogeneity, with values greater than 0.5 indicating a reasonable clustering structure), indicating effective clustering and high homogeneity within each cluster. Analyzing the clustering results reveals that research in the field of ocular drug delivery systems in the past 20 years includes 11 hot topics, namely #0 chitosan, #1 contact lenses, #2 glaucoma, #3 bioavailability, #4 cornea, #5 drug delivery, #6 corneal wound healing, #7 dexamethasone, #8 ocular, #9 solid lipid nanoparticles, and #10 nanostructured lipid carriers.

In CiteSpace software, a keyword timeline graph was generated to analyze the development trends of different research topics related to nanomediated ocular drug delivery systems from 2004 to 2023, as shown in Figure 9.Through Figure 9, it is

clear to see which research themes have gradually emerged and received widespread attention in recent years, and which themes are gradually losing their research fervour. This helps researchers understand the future direction of the field and potential research opportunities.

(1) Four research topics - #0 chitosan, #4 cornea, #8 ocular, #6 corneal wound healing - had already emerged around 2004 and have continued to the present, making them some of the longest-standing research topics in the field. Early high-frequency keywords such as nanoparticles, drug delivery, and ocular drug were commonly found in these four research clusters. In recent years, new keywords such as in situ gel, polymeric micelles, and antioxidant have also emerged, indicating that these research topics are perennial in the field, receiving continuous attention from researchers.

(2) Three topics - #1 contact lenses, #2 glaucoma, #7 dexamethasone - appeared earlier, with important related keywords including release, permeability, hydrogels, and eye. Among them, #1 contact lenses and #7 dexamethasone gradually lost research heat around 2020. The topic of glaucoma continues to be of interest.

(3) While three research clusters - #3 bioavailability, #9 solid lipid nanoparticles, #10 nanostructured lipid carriers - formed relatively late, the topics continue to receive widespread attention from researchers to this day. Specifically, the #10 nanostructured lipid carriers cluster has seen the emergence of numerous new keywords since 2016, such as stability and nanostructured lipid carriers.

An in-depth analysis of the reasons for the decline in the number of chitosan-based systematic studies, which may include technical bottlenecks, cost issues, and application limitations. The reasons for the gradual interest in lipid nanoparticle research may include aspects such as their unique physical and chemical properties, good biocompatibility and biodegradability, and potential applications in the treatment of ocular diseases.

DISCUSSION

In this study, a large body of literature on non-invasive nanoparticle drug delivery systems in the treatment of ophthalmic diseases was collected through extensive

literature search and screening. This literature was then systematically analysed and collated using bibliometric methods. As well as co-occurrence analysis and cluster analysis of keywords in the literature were performed. It was finally concluded that non-invasive nanoparticle drug delivery systems have significant advantages and development potential in the treatment of ophthalmic diseases.

The ocular surface, being in direct contact with the external environment, is a critical site for non-invasive drug delivery. Transocular surface drug delivery systems, with their non-invasive and efficient delivery characteristics, hold significant promise in ophthalmic pharmaceuticals[4]. In recent years, extensive investigations into ocular nanomediated drug delivery systems have been conducted across various laboratories, addressing a range of diseases and applications [7], thus establishing this research area as invaluable for further exploration. Bibliometric analysis provides a quantitative approach for reviewing and examining the existing literature in a specific field[11, 20-22]. Leveraging modern computational tools, the analysis results can be effectively visualized in clear, concise knowledge graphs. By analyzing the volume of publications, citations frequencies, prominent publishers, journals, and research themes in transocular surface drug delivery systems, key research trends and hot spots can be readily identified.

Although nanotechnology has shown great potential for drug delivery, patient compliance and comfort are still key factors affecting treatment outcomes. Particularly for drug delivery systems that require long-term wear or frequent use, such as contact lenses loaded with nanoparticles, patient acceptance and comfort are critical. Patient tolerance to contact lens wear varies with individual differences, and some may discontinue use due to discomfort or allergic reactions. Therefore, patient comfort and acceptance need to be taken into account when designing such drug delivery systems, and patient compliance needs to be improved by optimising the material, shape and wearing style.

Analysis of publications in this domain reveals a steady annual increase in research output, indicating sustained interest among researchers. A review of 695 articles

published between 2004 to 2023, spanning 58 countries/regions, 916 institutions, and 3405 authors, demonstrates the global engagement in this field. It is apparent from the co-occurrence network graph of institutions with a publication volume of 10 or more that universities are the primary platforms for research on transocular surface nanomediated drug delivery systems. Furthermore, extensive inter-institutional collaboration is evident, forming a significant cooperative network, which implies that researchers extend beyond small group studies to collaborate across multiple institutions, thereby advancing research through resource sharing. China lead in publication count in this field (n=220), though Spain and the United States exhibit higher average citations per article. This aligns with the significant contributions of the most prolific authors (Alvarez-Lorenzo, Carmen and Chanhan, Anuj) and their respective institutions (University of Santiago De Compostela and University of Florida). The research team led by Chanhan, Anuj is dedicated to advancing new methods to enhance the efficiency and compliance of ophthalmic drug delivery. Their innovations include novel nanostructured soft contact lenses capable of sustained drug release over days to weeks, significantly reducing drug loss to systemic circulation. Their research focuses on treating various ophthalmic diseases with contact lenses, including glaucoma, dry eye syndrome, chemical burns, and allergies. Recently, they have initiated research on drug delivery to the posterior segment of the eye, traditionally treated with intraocular injections, exploring the feasibility of using contact lenses for this purpose. Carmen Alvarez-Lorenzo, a Spanish pharmacist and researcher, primarily investigates the design and synthesis of polymer materials and their applications in drug release and nano drug delivery. Her research in the field of ocular drug release primarily aims to develop innovative release systems that enhance the efficacy of ocular drugs and reduce dosing frequency, with notable achievements in polymer ophthalmic controlled-release gels, nanoscale ophthalmic controlled-release systems, and temperature-sensitive controlled-release systems. The *International Journal of Pharmaceutics*, with an impact factor of 5.8, is an internationally renowned academic journal in the pharmacy field, dedicated to

publishing original research papers related to pharmaceutical formulations, controlled release systems, nanotechnology, biopharmaceutics, and drug delivery. This journal has published the most literature in this domain (n=57), significantly contributed to advancing research in the field. Notably, the journal with the highest average citations per article is the *Journal of Controlled Release*, with a current impact factor of 11.467, recognized as one of the most influential journals in the fields of pharmacy, biomaterials, and drug delivery. It covers a wide range of drug release topics, including the design and preparation of drug release systems, research on drug release mechanisms, and the development of drug transportation and delivery systems, serving as a high-quality academic platform for researchers to communicate and share research outcomes, thereby playing a pivotal role in advancing progress the field.

Through the co-occurrence analysis, cluster analysis, and timeline diagram analysis of keywords, it can be found that the research content of nanoparticle drug delivery systems of transocular surface in the past 20 years has mostly focused on chitosan in the early years, while more attention has been paid to cationic liposomes in recent years. This shift indicates that the application of nanomaterials transocular surface drug delivery has gradually changed from chitosan to cationic liposomes. Chitosan, one of the most widely studied raw materials in the field of nanomaterials, has shown chitosan-based nanoparticles exert antiviral and antibacterial effects after ocular surface applications, and deliver cyclosporine to exert immunomodulatory functions[23-25]. In recent years, chitosan-based nanomedicines have discovered that collagen/chitosan microspheres can be used for corneal epithelial regeneration [26], while a multifunctional hybrid hydrogel composed of silk fibroin and chitosan offers sustained drug release, proving effective in treating fungal keratitis[27]. In recent years, especially with the global epidemic of COVID19, LNP-based mRNA vaccines have been approved by the FDA for clinical use, which has greatly stimulated the research and application in related fields. A number of influential studies based on LNPs have demonstrated their long-term application potential. Baran-Rachwalska P et al showed that LNPs loaded siRNAs can efficiently target the corneal epithelium, thus

providing new insights for corneal and anterior segment disease treatment, and were also effective means for limited application of siRNA intervention[28]. In addition, another study used LNP-mediated genome editing of CRISPR/Cas9 for corneal gene editing in mice, presenting a promising strategy for addressing corneal gene mutations [29]. Given the existing LNP-loaded biologic drugs for clinical disease management, their potential for non-invasive delivery in the eye has important translational value for future treatments. Nanoparticle formulations have demonstrated a range of unique features and benefits in ocular drug delivery. The features include small size, high penetration capacity, and controlled drug release capability. In terms of mechanism, ocular delivery of nanoparticles involves several key steps. The first is the process of infiltration and penetration of the nanoparticles, where they need to overcome the barrier effects of the ocular tissues, such as the tight junctions of the corneal epithelium and endothelial cells. Second is the interaction of nanoparticles with ocular cells, including processes such as adsorption, endocytosis, and translocation. Finally, there is the release and action of the drug within the cell. Nanoparticle formulations can significantly overcome the limitations of traditional ocular drug delivery methods (e.g., eye drops, eye ointments, and eye tablets), such as short drug retention time, poor penetration, poor patient compliance, and possible side effects associated with frequent drug administration. By taking advantage of nanotechnology, these novel delivery systems are able to penetrate the corneal barrier more efficiently and prolong the retention time of the drug on the ocular surface, thereby improving drug bioavailability and therapeutic efficacy.

In contrast to nanoparticle drug delivery research in other organs (e.g., skin, lungs, intestines, etc.), research on ocular surfaces is similarly focussed on improving drug bioavailability, stability and targeting. However, the unique anatomy and physiological properties of the ocular surface (e.g., rapid tear drainage, corneal barriers, etc.) have led to research hotspots that are more focussed on addressing these specific challenges. For example, studies on corneal wound healing and dry eye are important in ocular surface drug delivery, whereas they may not be a primary focus in

drug delivery studies in other organs.

Earlier studies extensively explored contact lenses as carriers for nanomedicines delivery. A previous study showed that molecular-blotting techniques significantly increasing the timolol loading capacity of contact lenses, facilitating prolonged drug release [30]. Additionally, an effective and long-lasting vancomycin delivery system has been established by using vancomycin-controlled nanoparticle-containing contact lenses for ocular delivery, which provides a new idea for the treatment of infectious eye diseases[31]. In addition, a new type of polyacrylamide semi-interpenetrating network hydrogel constructed by quaternized chitosan and tannic acid has led to the creation of a new type of antibacterial and antioxidant contact lenses, which has realized the synergistic treatment of anti-infection and anti-oxidative stress [32].

Another promising technology that has gained the attention of researchers is microneedle (MNs), which has important academic and application value. MNs enable painless and efficient delivery of drugs through local tissues and have significant applications in eye disease interventions [33]. A 2007 study in a rabbit model showed that fluorescein sodium and pilocarpine [34] were effectively delivered using MNs. Moreover, corneal MNs can effectively achieve intracorneal drug delivery, and the dissolvable needles and detachable single MN technologies provide new insights into the local application of MNs[35, 36]. In addition to direct drug delivery, recent studies have explored the use of MNs to administer iron-based riboflavin nanoparticles and riboflavin, leveraging photothermal and cross-linking effects to treat bacterial keratitis and facilitate corneal cross-linking[37, 38]. These findings highlight the need to further investigate nanomaterial-based drugs with novel carriers, while also advancing clinical translational research by combining the latest drug delivery technologies. Glaucoma is an eye disease that causes damage to the optic nerve and is usually associated with increased intraocular pressure. Prolonged high intraocular pressure can lead to the gradual death of optic nerve fibres, eventually leading to loss of vision. Non-invasive nanoparticle drug delivery systems can deliver drugs through the ocular surface (e.g., conjunctival sac), utilising the permeability and

targeting properties of nanoparticles to deliver drugs directly to the ocular tissues, lowering intraocular pressure and reducing damage to the optic nerve. Drug candidates may include beta-blockers, carbonic anhydrase inhibitors, and others[39]. Age-related macular degeneration (AMD) is one of the leading causes of vision loss in the elderly and involves degeneration of the macular area in the central portion of the retina. Nanoparticle drug delivery systems can deliver anti-vascular endothelial growth factor (VEGF) drugs and other drugs directly to the retina through ocular surface delivery to inhibit neovascularisation and slow down the progression of AMD[40]. The future direction of non-invasive nanoparticle drug delivery systems will be to explore novel nanomaterials with better biocompatibility, stability and targeting to improve the efficiency of ocular drug delivery and therapeutic efficacy. Develop intelligent drug delivery systems that can respond to changes in the ocular microenvironment (e.g. pH, temperature, etc.) to achieve precise drug release and personalised treatment.

Based on the results of this study, we recommend that researchers further explore novel carrier materials for nanoparticles in ocular drug delivery to improve drug stability and bioavailability. For clinicians, we emphasise the need to pay close attention to patients' ocular reactions and potential toxicity issues when applying nanomedicines in clinical practice. In addition, we also advise our industry partners to give due consideration to cost-effectiveness and market demand when developing nanomedicine products to ensure their sustainability and competitiveness.

In conclusion, a bibliometric analysis utilizing VOSviewer (version 1.6.20) and CiteSpace (version 6.1) has been conducted on literature pertaining to noninvasive nanoparticle drug delivery systems of transocular surface over the past twenty years. This analysis considered factors such as publication volume, citation frequency, publishing institutions, journals, and research topics, providing a comprehensive understanding of this field. The novelty of this study lies in the fact that the research combines knowledge from a number of fields, including biomaterials science, pharmaceutical formulation technology, nanotechnology, and ophthalmic medicine,

providing an interdisciplinary perspective on the development of noninvasive transocular drug delivery systems. By analysing the research hotspots and trends, this study provides potential research directions for future researchers, such as exploring novel nanomaterials, optimising drug release systems, and improving drug bioavailability, which will help to promote the continuous progress in the field of non-invasive transocular drug delivery systems.However, it is important to acknowledge some limitations. The analysis relied exclusively on data from the Web of Science Core Collection (WoSCC), which may introduce a bias toward English-language publications, potentially overlook significant research in other languages. Additionally, the formatting requirements of the visualization software might exclude data sources. Citation metrics can fluctuate over time, influencing both results and their interpretation. While bibliometrics primarily provides quantitative data, it lacks qualitative insights into the content and quality of the research. These limitations should be considered when interpreting and applying this study's findings.

CONCLUSION

This study systematically summarises the current research status and trends in the field of non-invasive ocular surface nanoparticle drug delivery systems through bibliometric analysis. The results of the study show that this field has developed rapidly in recent years, especially in improving drug solubility, stability, corneal penetration and prolonging the residence time on the ocular surface, which demonstrates significant advantages. Countries such as China, the United States, India and Spain have made outstanding contributions to the research in this field, forming a group of core research forces. Keyword co-occurrence analysis revealed key research themes such as controlled release, cellular, dry eye, mechanism, expression and ocular drug delivery.

In the future, non-invasive ocular surface nanoparticle drug delivery systems will continue to explore novel nanomaterials to improve drug biocompatibility, stability and targeting. Meanwhile, optimising drug release systems and improving drug

bioavailability will also be a key research focus. In addition, with the development of smart technologies, the development of intelligent drug delivery systems that can respond to changes in the ocular microenvironment will become a new research direction. These efforts will help promote the continued advancement of ocular drug delivery technology and provide more effective and safer treatment options for patients with ocular diseases.

Conflicts of interest: Authors declare no conflict of interest.

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TABLES AND FIGURES WITH LEGENDS

Table 1. The top 10 productive authors

Rank	Author	Documents	Citations	Average Citation/Publication
1	Alvarez-Lorenzo, Carmen	16	475	29.69
2	Chauhan, Anuj	14	1274	91.00
3	Concheiro, Angel	13	384	29.54
4	Zhang, Junjie	10	133	13.30
5	Majumdar, Soumyajit	9	463	51.44
6	Nagai, Noriaki	9	195	21.67
7	Sheardown, Heather	9	167	18.56
8	Li, Xingyi	8	180	22.50
9	Ali, Asgar	7	467	66.71
10	Lai, Jui-Yang	7	465	66.43

Table 2. The top 10 productive counties

Rank	Country	Documents	Citations	Average Citation/Publication
1	China	220	5248	23.85
2	USA	112	5279	47.13
3	India	80	3078	38.48
4	Spain	65	3182	48.95
5	Canada	39	1423	36.49
6	Egypt	35	737	21.06
7	Italy	33	732	22.18
8	Portugal	30	963	32.10
9	Saudi Arabia	29	740	25.52
10	Iran	29	485	16.72

Table 3. The top 10 productive organizations

Rank	Organization	Documents	Citations	Average Citation/Publication
1	UNIV SANTIAGO DE COMPOSTELA	29	1859	64.10
2	UNIV FLORIDA	24	2253	93.88
3	SHENYANG PHARMACEUT UNIV	20	545	27.25
4	WENZHOU MED UNIV	18	204	11.33
5	CHINA PHARMACEUT UNIV	17	775	45.59
6	KING SAUD UNIV	16	443	27.69
7	CAIRO UNIV	16	394	24.63
8	UNIV BARCELONA	15	462	30.80
9	CHINESE ACAD SCI	14	559	39.93
10	SUN YAT SEN UNIV	14	378	27.00

Table 4. The top 10 productive journals

Rank	Organization	Documents	Citations	Average Citation/Publication
1	INTERNATIONAL JOURNAL OF PHARMACEUTICS	57	2563	44.96
2	PHARMACEUTICS	36	497	13.81
3	JOURNAL OF DRUG DELIVERY SCIENCE AND TECHNOLOGY	30	395	13.17
4	INTERNATIONAL JOURNAL OF NANOMEDICINE	22	814	37.00
5	JOURNAL OF CONTROLLED RELEASE	21	1290	61.43
6	DRUG DELIVERY	17	394	23.18
7	INTERNATIONAL JOURNAL OF BIOLOGICAL MACROMOLECULES	16	831	51.94
8	JOURNAL OF PHARMACEUTICAL SCIENCES	14	634	45.29
9	EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS	13	964	74.15
10	ACTA BIOMATERIALIA	12	394	32.83

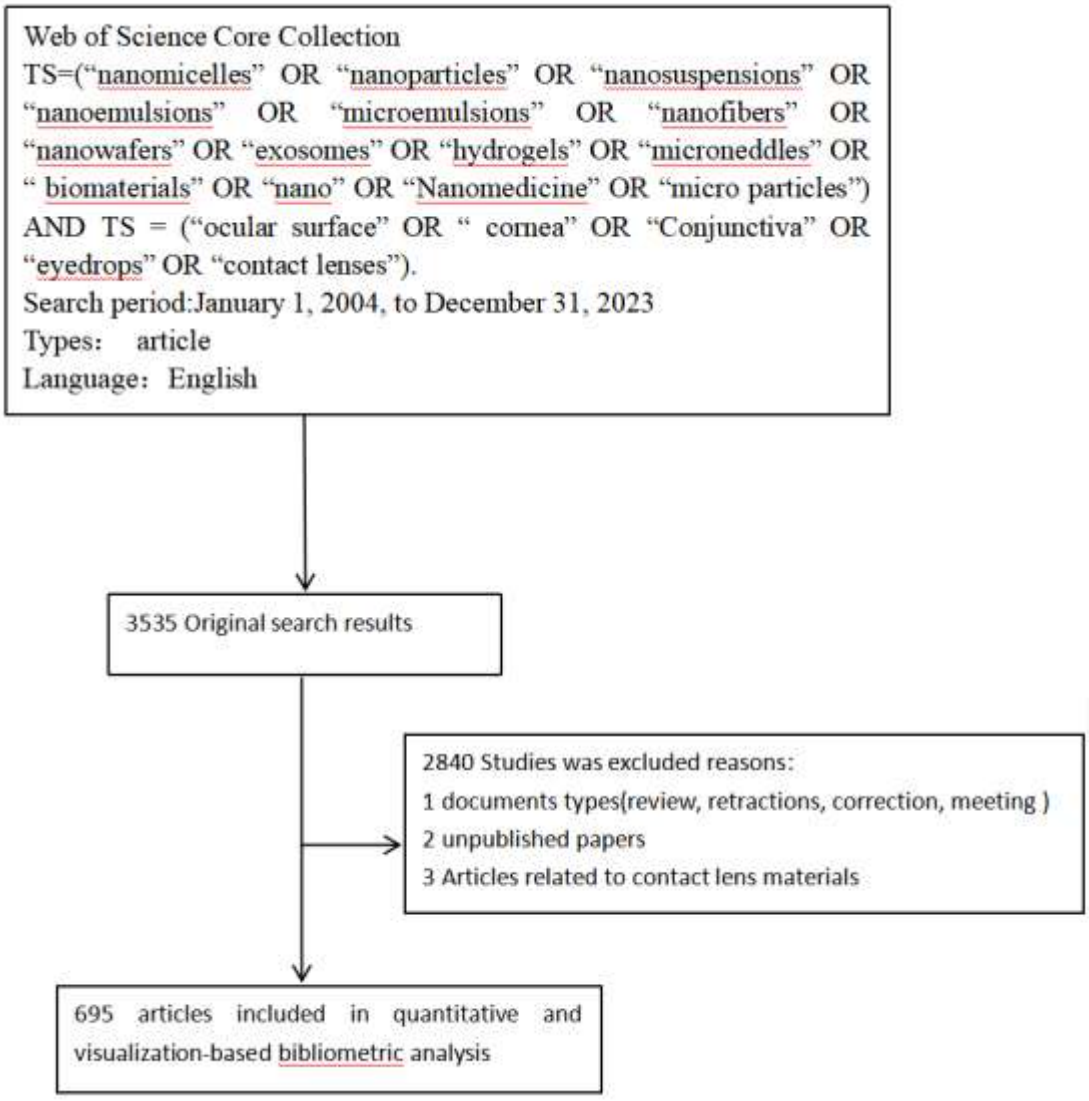

Figure 1. The data collection and retrieval strategy

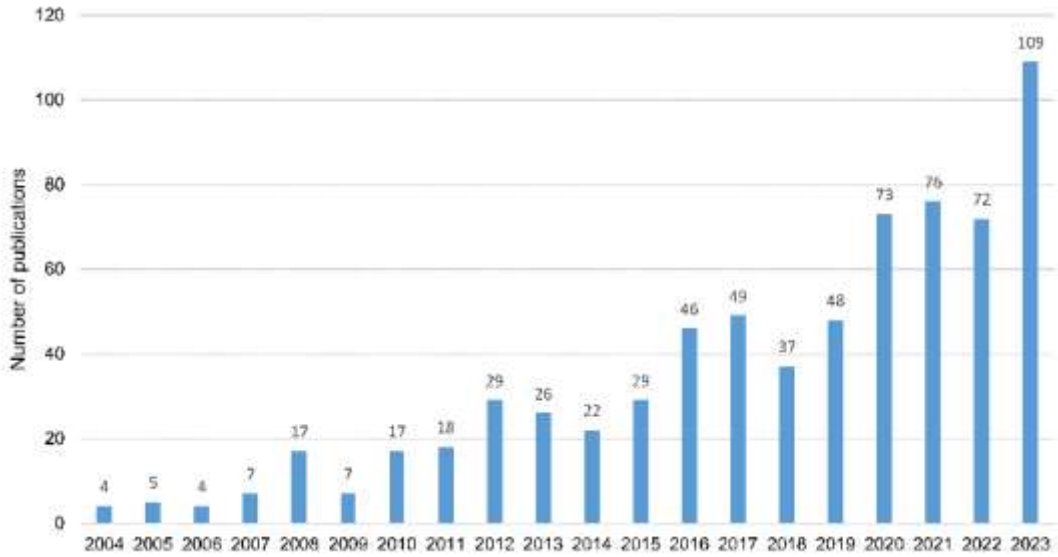

Figure 2. Distribution of publications from 2004 to 2023

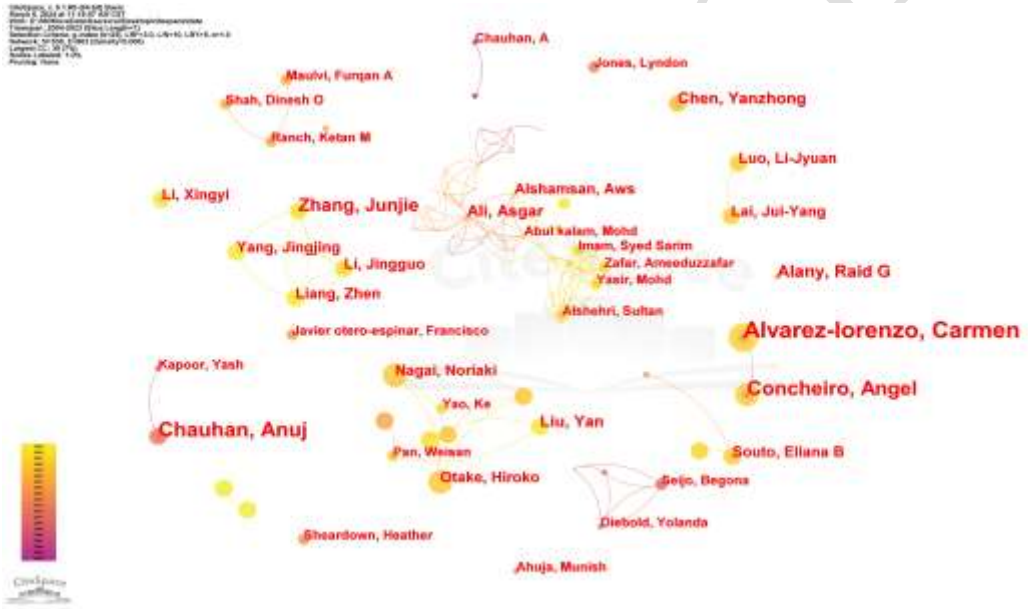

Figure 3. The co-authorship network of authors

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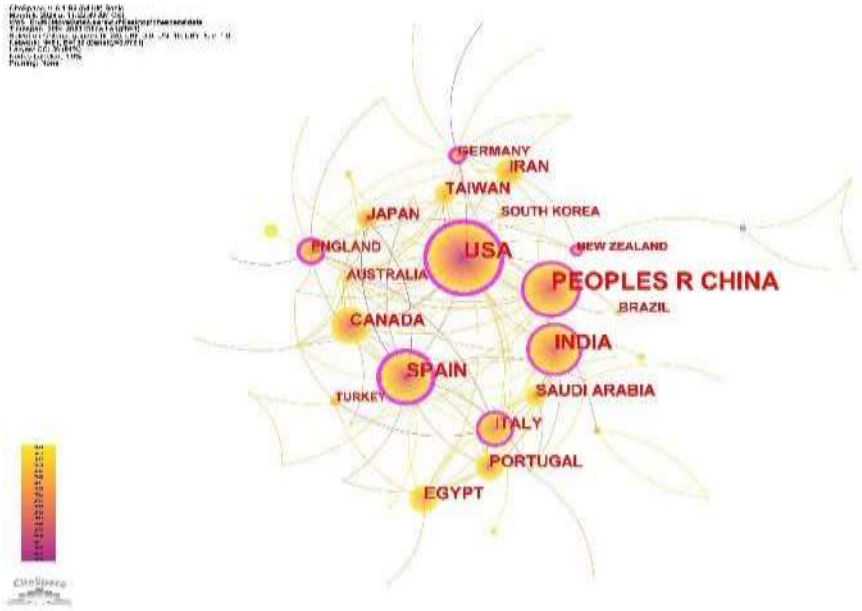

Figure 4. The co-authorship network of countries.

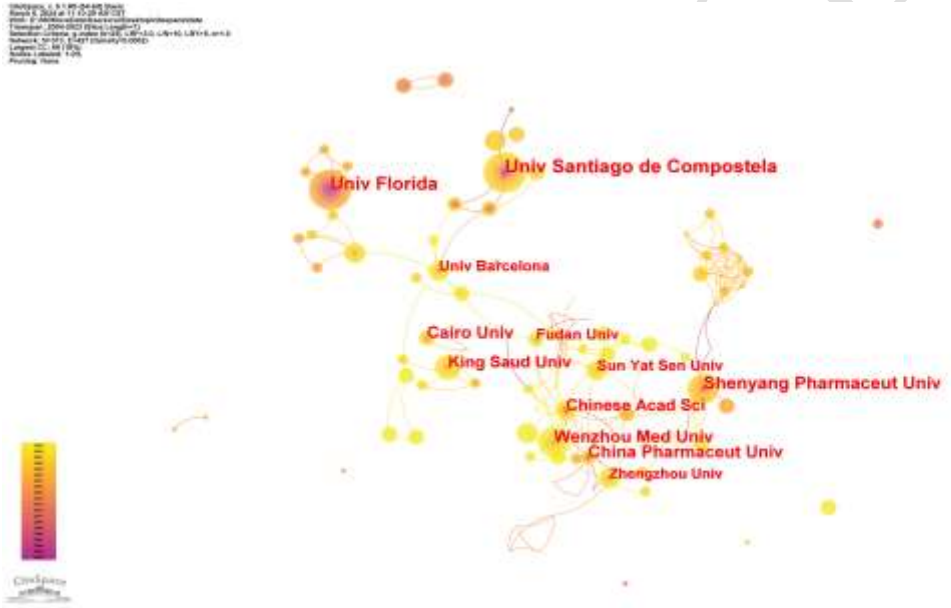

Figure 5. The co-authorship network of productive institutions.

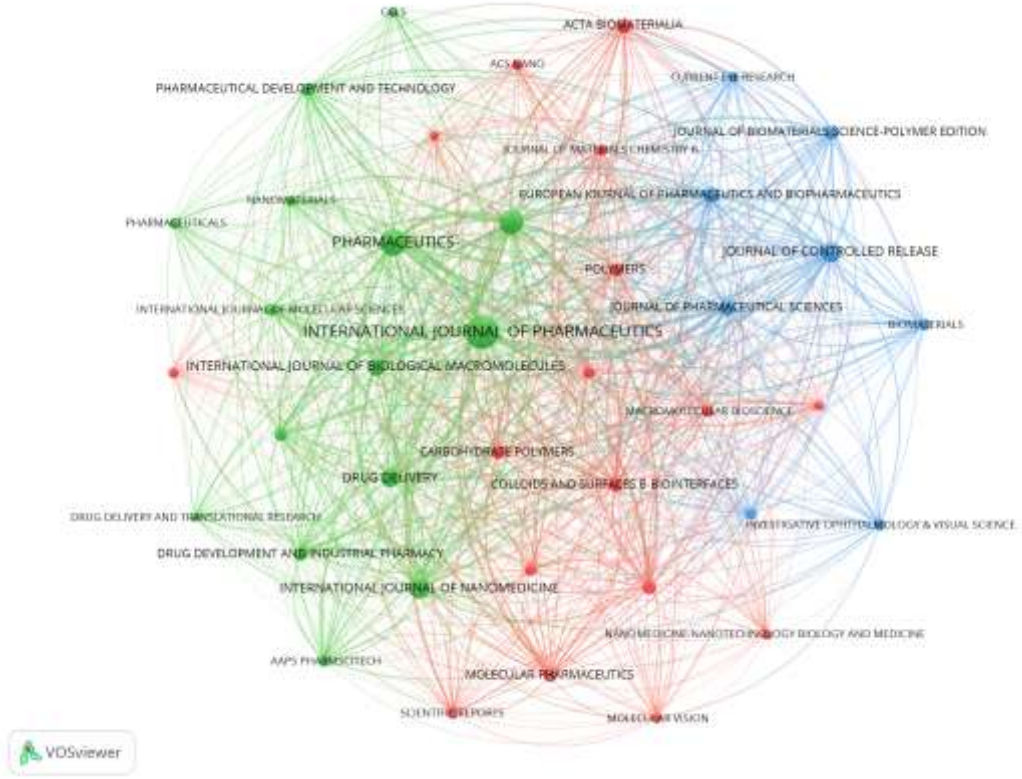

Figure 6. The co-authorship network of the journals.

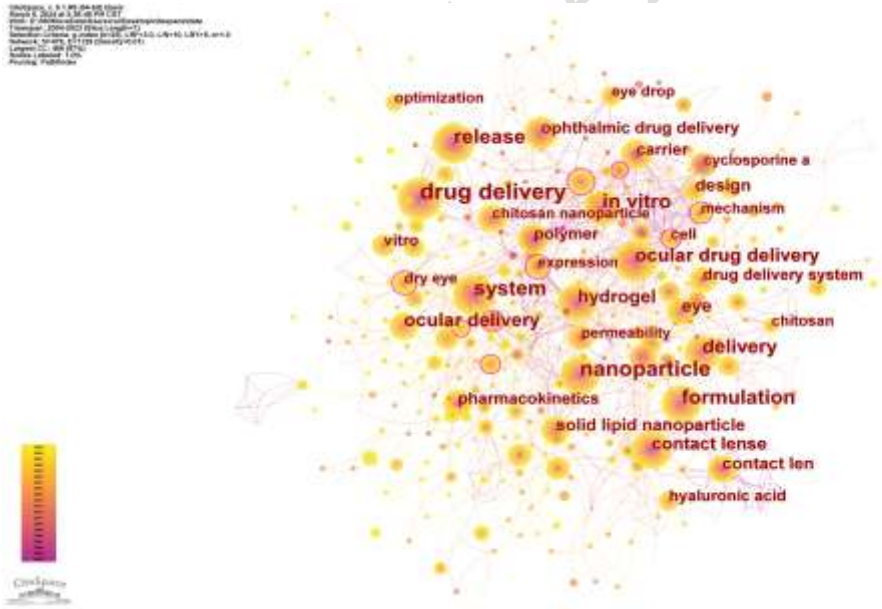

Figure 7. The co-occurrence analysis of keywords.

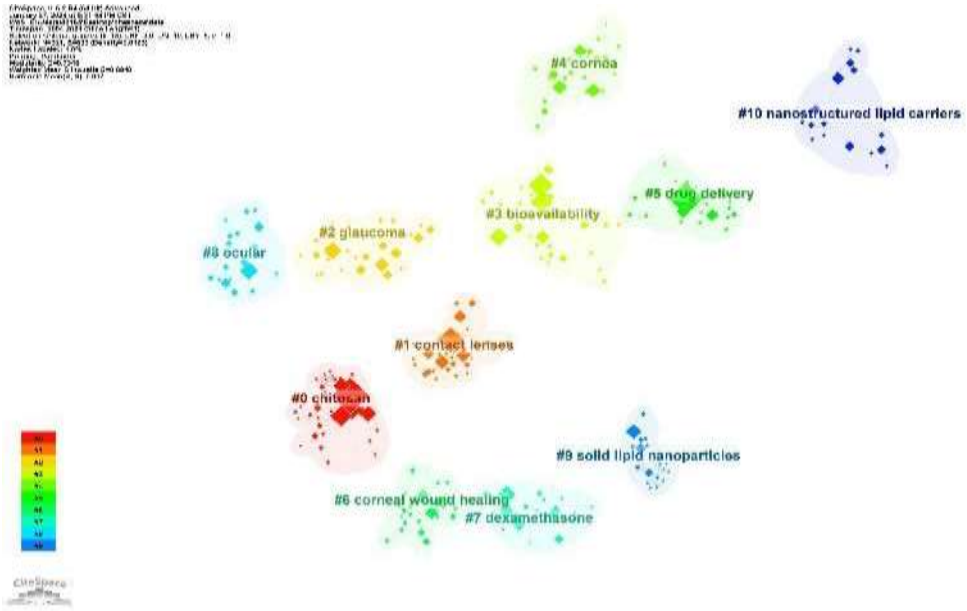

Figure 8. The co-occurrence analysis of the keyword cluster.

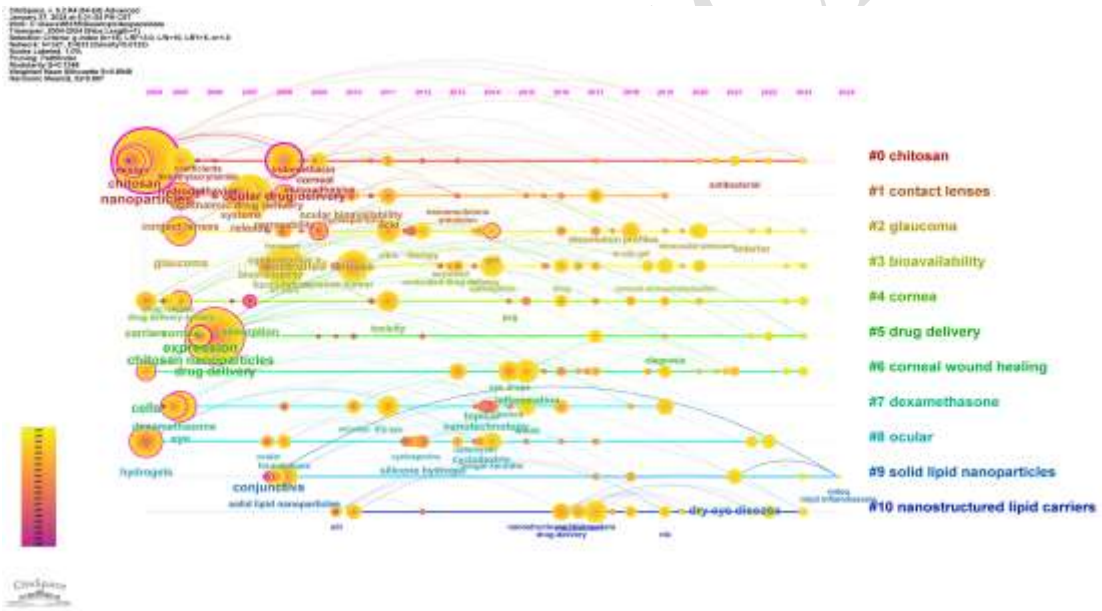

Figure 9. The co-occurrence analysis of the keyword timeline graph.